2016-04

IC-**3i** International PhD Program

# PhD thesis project

2017 Call for application

## Probing the Multiscale Dynamics of Individual Chromosomes in the Nucleus of Mammalian Cells with Advanced Imaging Techniques

## General information

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| **Call** | 2017 |
| **Reference** | 2016-04-DAHAN |
| **Keyword(s)** | chromosome dynamics, genome editing, live cell, Multifocus microscopy, light-sheet excitation |

## Director(s) and team

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| **Thesis director(s)** | Maxime Dahan |
| **Research team** | Light-based Observation & Control of Cellular Organization |
| **Research department** | UMR 168 - Physical Chemistry |

## Description of the PhD thesis project

Three-dimensional organization of the genome plays a crucial role in the regulation of gene expression and other nuclear functions (replication, repair). Genome organization has been mostly studied using a variety of biochemical, genetic and super-resolution imaging tools in fixed cells, often over large population. Yet, a proper understanding of the dynamic properties of chromatin and their influence on gene regulation is still missing. Thus, there is a pressing need for live imaging of chromatin dynamics at single cell level.

We propose to monitor, at the single chromosome level, the dynamics of individual fluorescent loci tagged using cutting edge genome editing tools. In order to access the spatio-temporal behavior of these loci at high resolution, novel imaging techniques combining light-sheet excitation (LSE) with multicolor multifocus microscopy (MFM) will be implemented to achieve high optical sensitivity and ultrafast 3D imaging capabilities. Multiple loci positioned at known relative genomic distances (from hundreds of kb to tens of Mbs) on the same chromosome will be simultaneously tracked in the 3D space of the nucleus of mammalian cells, over timescales ranging from milliseconds to hours. The dynamics properties of individual chromosomes will thus be measured and compared to polymer models derived from HiC data. Furthermore, the behavior of individual chromosomes will be correlated with transcriptional activity.

## International, interdisciplinary & intersectoral aspects of the project

The project stands at the crossroads between optics, physics, genome biology and cell biology. It is thus an intrinsically interdisciplinary project that will involve a variety of concepts, tools and methods coming from optical microscopy, genome editing and tagging, polymer modeling and cell biology. As it will involve the development of advanced microscopy technologies, the proposed project contains several technological aspects susceptible to be patented and to be transferred to start-ups or to SMEs. The project will benefit from multiple international collaborations established by the host laboratory, the PhD candidate will thus have the possibility to spend time in different research group around the world to discuss with renowned scientist in the field.

## Recent publications

1. Hajj B, El Beheiry M, **Dahan M**.
PSF Engineering in Multifocus microscopy For Increased Depth Volumetric Imaging
Biomed Opt Express. 2016 Feb 16;7(3):855-69. doi: 10.1364/BOE.7.000855.

2. Knight SC, Xie L, Deng W, Guglielmi B, Witkowsky LB, Bosanac L, Zhang ET, El Beheiry M, Masson JB, **Dahan M**, Liu Z, Doudna JA, Tjian R.
Dynamics of CRISPR-Cas9 Genome Interrogation in Living Cells.
Science. 2015 Nov 13;350(6262):823-6. doi: 10.1126/science.aac6572.

3. Normanno D, Boudarène L, Dugast-Darzacq C, Chen J, Richter C, Proux F, Bénichou O, Voituriez R, Darzacq X, **Dahan M**.
Probing the target search of DNA-binding proteins in mammalian cells using TetR as model searcher,
Nat Commun. 2015 Jul 7;6:7357. doi: 10.1038/ncomms8357.

4. Hajj B, Wisniewski J, El Beheiry M, Chen J, Revyakin A, Wu C, **Dahan M**.
Whole-cell, multicolor superresolution imaging using volumetric multifocus microscopy.
Proc Natl Acad Sci U S A. 2014 Dec 9;111(49):17480-5. doi: 10.1073/pnas.1412396111.

5. Abrahamsson S, Chen J, Hajj B, Stallinga S, Katsov AY, Wisniewski J, Mizuguchi G, Soule P, Mueller F, Dugast Darzacq C, Darzacq X, Wu C, Bargmann CI, Agard DA, **Dahan M**, Gustafsson MG.
Fast and sensitive multi-color 3D imaging using aberration-corrected multi-focus microscopy.
Nat Methods. 2013 Jan;10(1):60-3. doi: 10.1038/nmeth.2277.

## Expected profile of the candidate

The project is highly multi-disciplinary, applicants should have a strong motivation to explore and learn new technologies. The candidate will have to work with different people of different backgrounds, good communication skills are a plus. Good background or previous experiences in one of the following is desirable: optics, cell imaging, data processing, cell biology.